REMARKS

I. Status Of The Claims

Claims 1, 5-10, 12-14, 17 and 19 were pending and examined in the May 4, 2006 Office Action. Independent claims 1 and 12 have been amended in this reply. No new matter has been added. Accordingly, claims 1, 5-10, 12-14, 17 and 19 will be pending upon entry of this amendment.

II. Rejections under 35 U.S.C. § 112 – Indefiniteness

The Examiner has maintained his rejection of claims 12-14 as indefinite based upon the recitation of the term "T cell mediated autoimmune responses associated with type I diabetes." It is respectfully submitted that the amendment to claim 12 substituting this term with "T cell mediated tissue destruction associated with type I diabetes" as recited in current claim 1, overcomes this rejection. Support for this amendment is found in pending claim 1 and in the specification, for example, on page 3, lines 25-27 and lines 34-36.

Applicants respectfully submit that the amended claims recite "specific endpoints that can be measured" as requested by the Examiner and, thus, request withdrawal of the rejection (office action, dated May 4, 2006, p. 3).

III. Rejections Under 35 U.S.C. § 112 – Written Description

Claims 1, 5-10, 17 and 19 stand rejected under 35 U.S.C. § 112 for lack of written description. Specifically, the Examiner contends that the specification would not convey to one of

skill in the art that the applicants possessed an invention "wherein the anti-gp39 antibody or fragment binds to an epitope which is specifically bound by a monoclonal antibody produced by the 24-31 hybridoma" and that the subgenus of an "24-31 antibody epitopic specificity" is not supported by the specification (office action, dated May 4, 2006, p. 3).

Claim 1 has been amended to read that the anti-gp39 antibody or fragment binds to an epitope recognized by a monoclonal antibody produced by 24-31 hybridoma, ATCC Accession Number HB 11712. It is respectfully submitted claim 1 as amended meets the written description requirement. A person of ordinary skill in the art who read the present specification would conclude that the Applicants were in possession of the invention defined by the current claims at the time of filing the application. *Vas-Cath, Inc. v. Mahurkar,* 935 F.2d 1555, 1563 (Fed. Cir. 1991).

The specification discloses and describes several methods for making anti-gp39 antibodies and fragments thereof (specification, p. 4, l. 20 to p. 6, l. 18). Additionally, the specification discloses and describes that the "preferred anti-human gp39 antibodies of the invention are mAbs 24-31 and 89-76, produced respectively by hybridomas 24-31 and 89-76" which were "deposited under the provisions of the Budapest Treaty" (specification, p. 6, ll. 18-25). The method of making such antibodies or fragments thereof that bind to gp39 is fully described in the specification, as is a method for determining whether the claimed antibodies or fragments would bind to gp39 to an epitope as recognized by antibody 24-31 (specifcation, p. 4, l. 9 to p. 9, l. 22). The specification also specifically provides directions on how to produce recombinant anti-gp39 antibodies, such as chimeric and humanized antibodies by manipulating nucleic acids encoding an anti-gp39 antibody according to standard recombinant DNA techniques (specification, p. 6, ll. 26-38).

Further, the specification incorporates by reference the teachings of WO 95/06666 which issued into U.S. Patent No. 5,747,037 ("the '037 patent"). Thus, the disclosure of the '037 patent is considered part of the written description of the present application. The '037 patent teaches and describes the same techniques for making anti-gp39 antibodies, as well as describing the preferred deposited monoclonal antibody, designated 24-31. *See* '037 patent, col. 7, l. 13-col. 9, l. 25. The

'037 patent contains additional teachings including cross-blocking experiments used to show that show that the six monoclonal antibodies tested bound to different epitopes. *See* '037 patent, col. 26, ll. 25-54. The same experiments can be used to show that a monoclonal antibody binds to an epitope as recognized by 24-31. Further, it is respectfully submitted that the current amendment mirrors the language in allowed claim 1 of the '037 patent which has the same disclosure regarding the making of anti-gp39 antibodies and fragments. *See* '037 patent, claim 1.

In view of the above arguments, it would have been clear to a person of skill in the art that the Applicants possessed the claimed "anti-gp39 antibody or fragment [that] binds to an epitope recognized by a monoclonal antibody produced by 24-31 hybridoma, ATCC Accession Number HB 11712." Thus, Applicants respectfully submit that claims 1, 5-10, 17 and 19 meet the written description requirement of 35 U.S.C. § 112, first paragraph, and request withdrawal of the rejection.

IV. Rejections Under 35 U.S.C. § 112 – Enablement

Claims 12-14 have also been rejected for lack of enablement. Specifically, the Examiner asserts that it is unlikely that fusion proteins comprising a hypervariable region would have the required binding and inhibitory functions to prevent T cell mediated immune responses and tissue destruction. Further, the Examiner contends that the specification provides insufficient guidance regarding how to produce fusion proteins and antibodies as broadly defined by the claims.

This rejection is respectfully traversed.

Applicants submit that it would have been readily understood by one of ordinary skill in the art at the time of the present invention that the claimed recombinant antibodies bind to the same epitope as that to which the antibody from which the Complementarity Determining Regions (CDRs) are taken binds. That is, so long as a fusion protein contains CDRs which bind to the epitope bound by antibody 24-31, it may also contain a "hypervariable region of monoclonal

antibody 24-31" and bind to and inhibit functions to prevent T cell mediated immune responses and tissue destruction.

To this end, the specification refers to several documents, incorporated by reference therein, which explain that the use of "variable" and "hypervariable" regions in the construction of chimeric and humanized antibodies, respectively, was known at the time of the invention (specification, p. 6, l. 17; WO 95/06666, p. 9, ll. 1-20). The specification provides that a chimeric antibody is "a protein comprising at least the antigen binding portion of an immunoglobulin molecule (Ig) attached by peptide linkage to part of another protein" and discloses how to make such chimeric antibodies, *e.g.*, with antigen binding domains from one antibody (*i.e.*, CDR or hypervariable regions) and non-binding regions from another antibody (specification, p. 6, l. 3; EP 0 239 400, pp. 3 and 5). Further, the specification provides for the use of hypervariable regions (CDRs) of rat origin and framework regions from human origin (specification, p. 6, l. 3; WO 92/06193, paragraph bridging pp. 5-6).

For these reasons, Applicants submit that claims 12-14 are enabled and respectfully request withdrawal of the rejection.

V. Rejections Under 35 U.S.C. § 103 – Obviousness

The Examiner has maintained his rejection of claims 1, 5-10, 12-14, 17 and 19 as obvious in view of U.S. Patent No. 6,592,868 issued to Lederman *et al.* ("Lederman") in view of U.S. Patent No. 5,747,037 issued to Noelle ("Noelle"). The Examiner contends that the Lederman '868 patent which teaches the use of a CD40L-specific antibody for the treatment of diabetes renders the current claims obvious when combined with the disclosure in the Noelle '037 patent of monoclonal antibody 24-31.

The Examiner acknowledges that Lederman and Noelle do not teach "'T cell mediated autoimmune responses' per se", but alleges that both Lederman and Noelle clearly provide for

inhibiting cell-mediated inflammatory conditions, autoimmunity or diabetes with 5c8/CD40L-specific antibodies. Specifically, the Examiner contends that "[t]he prior art teachings of Lederman et al. is not limited to treating B cell immune responses only, given its teachings of inhibiting transplant rejection and autoimmune diseases such as diabetes." *See* Office Action, dated May 4, 2006, p. 6. Later the Examiner states, that while Lederman is silent about the prevention of T cell-mediated immune responses associated with type I diabetes, there is no "manipulative difference" in the method of the current claims and the prior art, and the applicants are merely claiming a new benefit of an old process. *See* Office Action, dated May 4, 2006, p. 7.

This rejection is respectfully traversed.

Applicants submit that the Examiner's assertions as to the teaching of the prior art are based upon incorrect assumptions. As shown below and in the accompanying Declaration of Edward A. Clark, Ph.D, an expert in the field, a person of skill in the art, given the state of the art in June of 1995, would not have arrived at the present invention by combining the teachings of Lederman and Noelle. The references must provide a reasonable expectation of success to support a *prima facie* case of obviousness. *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988). This expectation is not provided in an unpredictable art, absent some actual efficacy for the specifically claimed method. The instant specification provides exemplary results in a working example for a T cell-mediated autoimmune disease model. This demonstration of efficacy cannot be used in hindsight to render the invention obvious. *In re Dow Chemical Co.,* 837 F.2d 469 (Fed. Cir. 1988). Neither Lederman nor Noelle, alone or in combination, make such a demonstration.

As shown below, there are two distinct types of immune response, B cell-mediated or humoral, and T cell-mediated or cellular. It was known at the time of the invention that the immune response in type I diabetes has both a B cell-mediated and a T cell-mediated component. The presently claimed invention is to methods of inhibiting T cell-mediated responses in type I diabetes using an anti-gp39 antagonist. However, in June of 1995, it was not known that gp39 had a role in immune responses other than those involving T cell- B cell interactions, *i.e.,* humoral responses. Thus, one of skill in the art would have lacked a reasonable expectation of success in treating T cell-

mediated responses in type I diabetes with an anti-gp39 antibody from these early teachings. These references do not establish a *prima facie* case, which requires this expectation. MPEP § 2163. The expectation must be found in the prior art, not from the applicant's disclosure. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

The combined references also do not teach or suggest all of the claim limitations. The Examiner does appear to acknowledge this fact on page 6 of the Office Action. As will be shown in more detail below, "a method for preventing T cell mediated tissue destruction associated with type I diabetes" is missing from the cited references, either alone or in combination.

Lederman is limited to inhibiting B cell activation in autoimmune diseases, not T cell-mediated autoimmune diseases, as shown by the passage at column 10, line 62 to column 11, line 7 (emphasis added):

> This invention provides a *method of inhibiting B cell activation* to an animal which comprises administering to the animal an effective inhibiting amount of a pharmaceutical composition comprising the monoclonal antibody which specifically recognizes the activated T cell surface protein and a pharmaceutically acceptable carrier. For the purposes of this invention, an "effective inhibiting amount" of a pharmaceutical composition is any amount of the pharmaceutical composition which is effective to bind to a protein on the surface of the activated T cells and thereby *inhibit T cell activation of B cells*. In one embodiment of this invention, the B cells are resting B cells. In another embodiment of this invention, the B cells are primed B cells.

Thus, the Lederman describes the disclosed method strictly in terms of B cell activation.

There is no additional disclosure in the '868 patent that would expand the scope of this passage or the invention described therein to anything more than a method of inhibiting B cell activation because Lederman only teaches that the CD40L antagonists target helper T cell/ B cell interaction, not T cell-mediated immunological responses. *See* Declaration of Clark, ¶ 18. For example, Lederman presents data in Figure 11 showing that CD40L/gp39 is not expressed on CD8+ T cells, which are the T cells responsible for T cell-mediated responses. *See* below. Moreover, Lederman states that "[t]he monoclonal antibody described and claimed herein binds to *T cells*

which are interacting with B cells in the germinal centers of lymph nodes and *not to other T cells.*" (Lederman, col. 6, ll. 65-67 (emphasis added)). Lederman also states that "[f]or the purposes of this invention, 'activated T cells' are T cells capable of providing T cell helper function to resting B cells." (Lederman, col. 7, ll. 6-8). Moreover, the cell line used in Lederman, D1.1, is described as a T cell "capable of constitutively providing contact-dependent helper function to B cells." (Lederman, col. 9, ll. 4-9). These statements indicate that the Lederman '868 patent is concerned only with T cells providing helper function to B cells, and not concerned with other T cell function. *See* Declaration of Clark, ¶ 19. Thus, there is no teaching or suggestion in Lederman of inhibiting T cell-mediated immune responses, only B cell-mediated responses. Because these are two completely separate immune responses, in June of 1995, the suggestion of one would not have led a person of skill in the art to the other. *See* Declaration of Clark, ¶ 9.

T cells are divided into two broad categories, CD4+ T lymphocytes, which express the CD4 receptor ("helper" T cells) and CD8+ T lymphocytes, which express the CD8 receptor ("effector" or "cytotoxic" T cells). An immune response is initiated by the presentation of processed antigen by antigen-presenting cells (APCs) to T cells. Antigens are taken up by APCs and presented to T cells in association with either major histocompatibility complex (MHC) class I or class II molecules on the surface of the APC. CD4 binds class II MHC molecules, while CD8 binds class I MHC molecules. Peptides presented with class I molecules stimulate cytotoxic T cells to kill the cell from which the antigen was derived. In contrast, peptides presented with class II molecules stimulate helper T cells to generate further immune responses. *See* Declaration of Clark, ¶ 3.

Helper T cell stimulation of B cells leads to B cell activation, proliferation and differentiation into antibody-secreting cells. Aspects of the immune response mediated by antibodies are referred to as the humoral response. Humoral responses are so characterized when the immune response can be transferred from one experimental animal to another by transfer of antigen-specific antibodies. It is the inhibition of this helper T cell stimulation of B cells and humoral response that is disclosed in the Lederman '868 patent. *See* Declaration of Clark, ¶ 5.

In humoral immune responses, binding of antibodies to antigens can target an antigen for phagocytosis, lead to complement fixation, and/or attract further inflammatory cells. These mechanisms can lead to cellular injury. An example of an antibody-mediated disease is systemic lupus erythematosus, a disease characterized by antibodies to DNA, ribonucleoproteins, and other non-organ-specific molecules (specification, p. 1). *See* Declaration of Clark, ¶ 6.

In contrast to humoral immune response, T cell-mediated response are not mediated by autoantibodies and represent an immune response that is independent of B cell activation. Immune responses of this type can be transferred in experimental models by transfer of T cells as opposed to antibodies. An example of a T cell-mediated autoimmune disorder model is EAE, an animal model for multiple sclerosis (MS), where T cells reactive to myelin cause demyelination of the brain and spinal cord. EAE can be transferred from diseased animals to healthy ones by the transfer of T cells from the diseased animals. Another model of T cell-mediated autoimmune disease is the NOD mouse. This mouse spontaneously develops insulitis and diabetes, and the diseases can be transferred from the diseased animal to the healthy one by the transfer of T cells. *See* Declaration of Clark, ¶ 7. *See also* Exhibits B and C to Clark Declaration.

Against this background, it clearly can be seen that B cell-, *i.e.*, humoral, and T cell-, *i.e.*, cellular, mediated immune responses have completely different mechanisms of action. Thus, the disclosure of the current application provides an entirely unexpected result, specifically, that inhibition of a T cell receptor previously shown to be necessary for the disruption of T cell-B cell interactions only, is capable of inhibiting the symptoms and/or progression of a disease that is non-B cell mediated. At the time of the invention, one of skill in the art would not have recognized that a gp39 antagonist would have an effect on T cell-mediated disease because that mechanism of disease is independent of B cell activation, which was considered the primary role of gp39. *It was not known in the art in June of 1995 that gp39 had any role in non-B cell immune responses. See* Clark Declaration, ¶ 9.

As set forth in the Declaration of Dr. Clark, in June of 1995, there were some reports of an anti-gp39 antagonist blocking the B cell production of T cell-dependent antibodies (Clark

Declaration, ¶ 10; Exhibits D and E to Clark Declaration). However, at this time there were no published reports of the role of gp39 (CD40L) in regulating non-B cell immunity. In late 1995, a few studies were starting to be published that showed a role of gp39 (CD40L) in regulating non-B cell immunity, and that a gp39 antagonist could, in certain situations, block CD4+ T cell-mediated resistance that did not involve B cells. *See* Clark Declaration, ¶ 11; Exhibit F to Clark Declaration). However, even in 1996, it was still uncertain what role, if any, CD40L had in the T cell immune response, and studies were beginning to be undertaken to determine such. *Id.;* Exhibit H to Clark Declaration.

Thus, at the time of the filing of the present application, the state of the art was such that it was not recognized that gp39 had a role in non-B cell immune responses and a teaching of using an anti-gp39 antibody for blocking B cell-mediated responses would not render the use of an anti-gp39 antibody to block non-B cell, *i.e.,* T cell-dependent, immune responses, obvious to a person of skill in the art. *See* Clark Declaration, ¶¶ 9 and 12.

The Examiner further asserts because Lederman discloses that 5c8 antibodies can be used for treating diabetes, Lederman discloses the present invention. It is respectfully submitted that the Examiner's assertion is incorrect.

The Lederman '868 patent mentions diabetes exclusively in the *context of B cell activation, not in the context of preventing a T cell mediated autoimmune disorder* (Lederman, col. 11, ll. 18-35). There is no mention of preventing T cell-mediated autoimmune disease damage in relation to type I diabetes in Lederman. While Lederman lists diseases that can be treated by the disclosed method, most of the diseases listed are known to be primarily B cell-mediated. While diabetes and transplant rejections are included in the list, a fair reading of Lederman is that it merely implies that diabetes mellitus, as well as transplant rejections, have B cell-mediated components that can perhaps be treated by the 5c8 antibody. It was known in the art in June of 1995 that the immune response in both transplant rejections and type I diabetes had both B cell- and T cell-mediated components. *See* Declaration of Clark, ¶ 13. However, nothing in the teachings or disclosure of

Lederman suggests that the disclosed method can be used to treat the T cell-mediated aspects of the disease. *See* Declaration of Clark, ¶ 18 and 19.

The T cell-mediated component of type I diabetes is the T cell-mediated destruction of beta cells. In T cell-mediated diabetic complications, autoreactive $CD8^+$ cytotoxic T cells recognize peptides from a beta cell-specific protein, bind to the beta cells, and selectively destroy these cells. *Antibodies are not necessary for this response.* Thus, diabetic autoimmune disease may involve humoral-mediated and/or cell-mediated tissue damage, but the mechanisms of damage are distinct. Diabetic tissue damage or dysfunction mediated by B cells would have been considered treatable by application of CD40L antagonists that were known in June of 1995 to prevent T cell activation of B cells. *However, destruction of beta cells by cytotoxic T cells, and inflammation caused by T cell mediated activation of other immune cells such as macrophages, would not have been considered treatable or preventable by administration of CD40L antagonists in June of 1995. See* Clark Declaration, ¶ 14.

The first study even suggesting CD40L-CD40 interactions in T cell-mediated aspects of diabetes was published almost a year and half after the filing date of the present application in November of 1997. The authors of the study stated that while CD40-CD40L interactions in B cell-mediated autoimmune disease had been reported, the possibility that CD40-CD40L interactions play a role in T cell dependent autoimmune disease "remains untested." *See* Exhibit K to Clark Declaration, page 4620; *see also* Clark Declaration, ¶ 15.

The Examiner, while admitting that Lederman only teaches B cell activation, asserts that it was known in the art that "*CD40L was expressed on important activated CD4+ T cells* that regulated various immune responses and that CD40L was targeted in conditions and disorders know to be cell-mediated at the time the invention was made." *See* Office Action, dated May 4, 2006, page 8 (emphasis added). The Examiner also states that the prior art teaches "the advantages of anti-CD40L antibodies to inhibit immune responses by targeting the CD40L on T helper cells in therapeutic modalities of immunosuppression at the time the invention was made." *Id.* However, as stated above, the T cell-mediated response in type I diabetes involves autoreactive CD8+ cytoxic T

cells, not CD4+ T helper cells. *See also* Clark Declaration, ¶¶ 3 and 14. The disclosure of Lederman that CD40L was expressed on helper T cells would not lead a person of skill in the art to the use of an anti-CD40L antibody in T cell-mediated immune response nor would it give rise to any reasonable expectation of success to do so because these cells are not involved in this response. *See* Declaration of Clark, ¶¶ 3, 12 and 14.

Autoimmune diseases are often the products of both B cell- and T cell-mediated responses. But while it would have been expected, in June of 1995, to successfully treat the B cell/humoral/antibody-mediated responses using an anti-gp39 antagonist which interferes with the helper T cell-B cell interactions, it would have not been expected to successfully use the same method to treat T cell-mediated aspects of autoimmune disease. As shown above, in June of 1995, the art was such that gp39 was thought only to be involved in T cell- B cell interactions. Its potential role in non-B cell immune responses was only elucidated after the effective filing date of the present application. More importantly, the role of gp39 in the T cell-mediated aspects of diabetes remained untested and unknown at least a year after the filing date of the present application. Thus, one of skill in the art would not have been lead to the presently claimed invention of using an anti-gp39 antibody to treat T cell-mediated aspects of diabetes based upon the teachings in Lederman of antagonists of the helper T cell-B cell interaction. There was simply not enough knowledge in the art at the time. Indeed, the state of the art would have lead a person of skill to the correct conclusion that Lederman only teaches the use of an anti-gp39 antibody in the treatment of B cell-mediated autoimmune disease. Thus, the present invention is unexpected in light of the knowledge in the art in June of 1995.

Additionally, the disclosure of Lederman would not even teach a person of skill in the art to treat the B cell-mediated diseases because their model systems are flawed. There are no data anywhere in the Lederman '868 patent showing the effect of monoclonal antibody 5c8 on autoimmune responses or autoimmune diseases. Indeed, there are no data showing the effect of normal human T cells expressing what is called T-BAM on an immune response *in vitro* or *in vivo*. *See* Clark Declaration, ¶ 20.

The Lederman '868 patent does not teach anything about the treatment of autoimmune disease because it uses a human T cell line, Jurkat, which proliferates continuously in culture. One of skill in the art would not have used Jurkat T cells to study the role of monoclonal antibody 5c8 on autoimmune responses or autoimmune diseases because Jurkat is a transformed T cell leukemia line and cannot be used to induce antigen-specific responses *in vitro* or *in vivo*. At the time of the present application, one of skill in the art would have recognized that signaling a Jurkat T cell line with an anti-CD3 monoclonal antibody, was not the same as signaling with an antigen and using the Jurkat cell line to activate B cells was not a good model for the interactions that could occur between normal T cells and B cells. *See* Declaration of Clark, ¶¶ 21 and 22.

Additionally, in the experiments where normal T cells are used in Lederman, non-physiologic stimuli, such as PMA and pokeweed antigen, are used to activate the T cells. (Lederman, Example 6, col. 23, ll. 38-53; Example 7, col. 23, l. 55 to col. 24, l. 29). Thus, Lederman does not demonstrate that CD40L is induced on normal T cells by antigens. *See* Declaration of Clark, ¶ 23.

The '868 patent does not provide evidence showing that the 5c8 anti-CD40L monoclonal antibody binds to cells other than human T cells activated by non-physiologic stimuli and the Jurkat human T cell line, and certainly provides no evidence that the 5c8 antibody can affect an autoimmune disease in an animal including humans. There are no functional data in Lederman using T cells activated with physiologic stimuli, *i.e.,* antigen, and no data assessing the role of an anti-CD40L antibody *in vivo* which would be essential to know if the antibody could inhibit autoimmune disease. *See* Declaration of Clark, ¶ 24.

For all of the reasons set forth above, Lederman does not teach or suggest the currently claimed invention of "a method of preventing for preventing T cell-mediated tissue destruction associated with type I diabetes" either alone or in combination with Noelle.

Moreover, the disclosure of the Noelle '037 patent would not lead a person of skill in the art to treat diabetes with anti-gp39 antagonists, either alone or in combination with other prior art.

Noelle does teach a method for inducing antigen-specific T cell tolerance and a means to block allogeneic T cell responses as measured by graft versus host disease (GVHD) using anti-gp39 monoclonal antibodies. One skilled in the art would have thought that this treatment might be pertinent for the treatment of diabetes to the extent that the method in Noelle involves pancreatic allografts. However, this would not suggest that the underlying disease of diabetes could be directly treated with an anti-gp39 antagonist. Nor was it known in June of 1995 that pancreatic allograft rejection could be treated with anti-CD40L antagonists. In short, the Noelle '037 patent concerns the induction of antigen-specific T cell tolerance that would applicable to allogeneic transplantation or autoimmune disease where the autoantigens are clearly defined. *See* Declaration of Clark, ¶ 17.

Thus, the teachings of Lederman and Noelle, either alone or in combination, do not teach or suggest every claim limitation. Furthermore, as shown above, the state of the art in June of 1995 was such that the currently claimed invention was unexpected and a person of skill in the art would not have had a reasonable expectation of success in treating T cell-mediated immune responses associated with diabetes based upon the teachings of Lederman and Noelle.

It is also respectfully submitted that the evidence submitted in with the April 1, 2005 reply (Noelle Declaration (Exhibit D) and Exhibits B and C) as to the superior results of the 24-31 antibody *in vivo* over the 5c8 antibody has not been accorded its due weight. In addition to being therapeutically safe by not causing thomboses (contrary to hu5c8), the antibodies of the presently claimed method block binding of CD40 to gp39 *in vivo* more effectively than 5c8. Due consideration is required of objective evidence of superior results.

In view of the above arguments and amendments, Applicants submit that Lederman and Noelle, taken alone or in any combination, do not render the claimed invention obvious and, thus, respectfully request withdrawal of the rejection.

VI. Conclusion

In view of the above amendments and remarks, it is respectfully submitted that the pending claims are now in condition for allowance and such action is earnestly solicited. If the Examiner believes that a telephone conversation would help advance the prosecution in this case, the Examiner is respectfully requested to call the undersigned attorney at (212) 527-7601. The Examiner is hereby authorized to charge any additional fees associated with this response to our Deposit Account No. 04-0100.

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Respectfully submitted,

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